REMARKS

Claims 20 – 32 are pending. Claims 20 – 21 were previously withdrawn. No amendment has been made.

In a telephone interview dated November 13, 2007, the Examiner indicated that in the Final Office Action dated August 6, 2007, claim 22 was incorrectly listed as unexamined. The undersigned and the Examiner agreed that claim 22 was examined and was rejected under 35 U.S.C. §103(a).

The Advisory Action dated December 11, 2007 indicates that written description and enablement rejections under 35 U.S.C. § 112, 1st paragraph have been overcome.

Claim rejections - 35 U.S.C. §103

Claims 22 – 32 remain rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Smeekens et al. (US 6,147,280) in view of DeAngelis et al. (Hyaluronan Synthase of Chlorella Virus PBCV-1, *Science* 1997: Vol. 278., pp. 1800 – 1803) and further in light of Akasaka (US 4,801,539) and Mattes et al. (US 5,985,668). Applicants traverse the rejections.

First, there is a lack of motivation to combined the references cited. The Office Action contends that one skilled in the art would have been motivated to generate the claimed invention because the motivation to combine is "the scalable and plant based production of carbohydrates as taught by Akasaka" and "it is well known that reactor-based production using bacterial leads to the contamination by bacterial hemolytic toxins such as streptolysin as taught by Akasaka (column 1, lines 15-60) and that reactor-based production is not scalable and is more expensive than plant based production as taught or suggested by Mattes and by Smeekens (Mattes, et al., @ column 1, line 20-26; Smeekens @ column 3, line 4)." Final Office Action, page 6. Applicants respectfully point out that plant-based production of carbohydrates are NOT taught by Akasaka or Mattes (U.S. Patent No. 5,985,668).

A prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); MPEP 2141.02 VI. Akasaka discloses that producing hyaluronic acid using Streptococcus bacterial strains is cheaper than isolating hyaluronic acid from the hyaloid liquid (col. 1, lines 14-32), but

the by-product, streptolysin, is undesirable (col. 1, lines 37-51). However, Akasaka does not teach or suggest transforming a plant cell to produce hyaluronic acid. Instead, Akasaka teaches a fermentation method using a mutant strain of Streptococcus. See col. 1, lines 62-65.

Similarly, Mattes discloses that the industrial method of producing two disaccharides using immobilized bacterial cells is problematic because unwanted monosaccharides are also produced. Col. 1, lines 14-25. Yet Mattes does not suggest transforming a plant cell to produce the desired disaccharides. Instead, Mattes teaches a cell-based method using mutated cells. See col. 7, lines 11-20 and claim 21.

Thus, neither Akasaka or Mattes teaches or suggests any non-reactor based production method, let alone the method as recited in the present claims. One of ordinary skill in the art, in view of Akasaka and Mattes, would at most have been motivated to use a reactor-based method using mutated cells to produce carbohydrates.

Moreover, Smeekens, alone or in combination with other cited references, does not provide a motivation to transform a plant cell to produce a carbohydrate other than oligosaccharides with a specific formula. The Final Office Action contends that Smeekens teaches more than just oligosaccharides and teaches or suggests more than just fructans. Applicants disagree.

Smeekens discloses that in WO 89/12386 the SacB gene of *Bacillus subtillis* is incorporated in plants to modify the fructan patterns in these plants, and that the process is related to the production of high-molecular polysaccharides. However, WO 89/12386 merely teaches the increased production of naturally occurring carbohydrates in the plants. Indeed, WO 89/12386 teaches away from "unfamiliar" carbohydrate polymers because the plant is unlikely to possess an enzyme capable of degrading the unfamiliar polymer. See page 7, lines 9-16. As such, WO 89/12386 does not teach or suggest, by itself or through Smeekens, transforming a plant cell to produce a non-naturally occurring carbohydrate such as hyaluronic acid, as recited in the present claims.

The teaching of Smeekens is limited to the plant-based production of highly specific oligosaccharides. Applicants point out that although some fructosyltransferases are capable of converting sucrose into high-molecular fructans, Smeekens only teaches transforming a plant cell

using a oligosaccharide-producing fructosyltransferase gene. See Examples 1 and 2. Additionally, most of the advantages associated with the plant-based production method in Smeekens only applies to the plant-based production of oligosaccharides. See col. 2, line 53 – col. 3, line 4. Therefore, one of ordinary skill in the art would not have been motivated to modify Smeekens to transform a plant cell to produce a polysaccharide, for which most of the advantages of Smeekens' method would not apply.

The Final Office Action contends that Smeekens teaches more than just oligosaccharides and teaches or suggests more than just fructans because it is well known to the ordinarily skilled artisan that plants already contain starch, a large polymer of sugars. This contention is incorrect because the fact that plants contain starch is irrelevant to plants' capability of incorporating foreign gene to produce a non-naturally occurring carbohydrate. For example, the foreign gene may interfere with the normal functions of the plant, and the plant may not even have enough sugar substrate available to produce the non-naturally occurring carbohydrates. The teaching of Smeekens is limited to a specific kind of enzyme, namely fructosyltransferase, that uses a specific kind of substrate, namely sucrose. The products of Smeekens are oligosaccharides with the formula GmFn, wherein G represents glucose and F represents fructose, and wherein m equals 0 or 1 and n is an integer larger than or equal to 0. See col. 1, ll. 26-43. Smeekens does not teach or suggest using any other enzyme, such as a hyaluronic acid synthase (which is a glucosyltransferase), or using any other substrate, such as the sugar precursors of uridine-5'-diphosphoflucuronic acid (UDP-GlcA) and uridine-5'-diphospho-N-acetylglucosamine (UDP-GlcNAc).

Further, there is no reasonable expectation of success even if Smeekens were to be modified, at least because the substrates involved in synthesizing the oligosaccharides of Smeekens and the hyaluronic acid recited in the present claims are different. The substrate for synthesizing the oligosaccharides of Smeekens is sucrose, which is available naturally in abundance in plants. See Smeekens, sol. 5, lines 32-36. Additionally, Applicants hereby attach an article (Gerrits et al., *Sucrose Metabolism in Plastids*, Plant Physiology, Vol. 125, pp. 926-934, 2001) showing that sucrose is present in large amount in plants. See Figures 2 and 4. The use of sucrose by the introduced fructosyltransferase is not likely to interfere with cells' normal functions because there is enough sucrose to be used in the natural processes. On the other hand,

the substrates needed for the synthesis of hyaluronic acid are two sugar nucleotides: UDP-GlcA and UDP-GlcNAc. The content of sugar nucleotides in plants is small. See page 2908, left column, last paragraph of the attached article (Hayashi and Matsuda, Sugar Nucleotides from Suspension-cultured Soybean Cells, *Agric. Biol. Chem.*, 45 (12), 2907-2908, 1981). Plants that do not naturally produce hyaluronic acid do not have a large pool of the sugar precursors, GlcA and GlcNAc, of UDP-GlcA and UDP-GlcNAc, respectively. GlcA and GlcNAc are used by cells for processes such as cell wall synthesis. Therefore, if a foreign gene introduced to a plant uses the limited supply of GlcA and GlcNAc to produce hyaluronic acid, the process would be expected to interfere with the normal growth of the plant because the GlcA and GlcNAc may be depleted and no longer available for their original purposes, such as cell wall synthesis. As such, one of ordinary skill in the art would not have had reasonable expectation of success transforming a plant cell using a hyaluronic acid synthase gene. However, the present inventors have found, surprisingly, that by using the methods as recited in the claims, hyaluronic acid can be produced without having harmful effects on the transformed plants.

The deficiency of Smeekens, Akasaka, and Mattes is not cured by DeAngelis because DeAngelis, either alone or in combination with the other cited references, does not teach or suggest transforming a plant cell to produce hyaluronic acid.

Therefore, for at least the reasons stated above, a *prima facie* case of obviousness has not been established. Withdrawal of the rejections is requested.

CONCLUSION

The claims are believed to be allowable.

The Examiner is invited to contact the undersigned at (202) 220-4200 to discuss any matter concerning this application.

In the event that the filing of this paper is deemed not timely, Applicants petition for an appropriate extension of time. The Office is authorized to charge any additional fees or credit any overpayments to deposit account 11-0600 of Kenyon & Kenyon LLP.

Respectfully submitted,

Dated: February 6, 2008 By: _____

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